PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07H 17/08	A2	(11) International Publication Number: WO 99/32500
		(43) International Publication Date: 1 July 1999 (01.07.99)

(21) International Application Number: PCT/EP98/08320

(22) International Filing Date: 18 December 1998 (18.12.98)

(30) Priority Data:

9726991.4	22 December 1997 (22.12.97)	GB
9726992.2	22 December 1997 (22.12.97)	GB

(71) Applicant *(for all designated States except US)*: BIOCHEMIE S.A. [ES/ES]; Ap. de Correos, 97, E–08400 Granollers (ES).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BOSCH, Immaculada [ES/ES]; Raval Cortines, 21, E–08500 Vic (ES). CENTELLAS, Victor [ES/ES]; Narcis Monturiol, 2–b, E–08440 Cardedeu (ES). DIAGO, José [ES/ES]; Calle Josep Carner, 43–5–a, E–08400 Granollers (ES).

(74) Agent: BECKER, Konrad; Novartis AG, Patent– und Markenabteilung, Lichtstrasse 35, CH–4002 Basel (CH).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: INTERMEDIATES IN MACROLIDE PRODUCTION

(57) Abstract

Erythromycin A oxime wherein the hydroxyl group of the oxime group is in reacted form resulting from reaction with a strong organic base or with a silylation agent; a process for its production and its use as an intermediate in the production of macrolides of the erythromycin type, such as roxithromycin, clarithromycin, azithromycin and similar compounds.

FOR THE PURPOSES OF INFORMATION ONLY

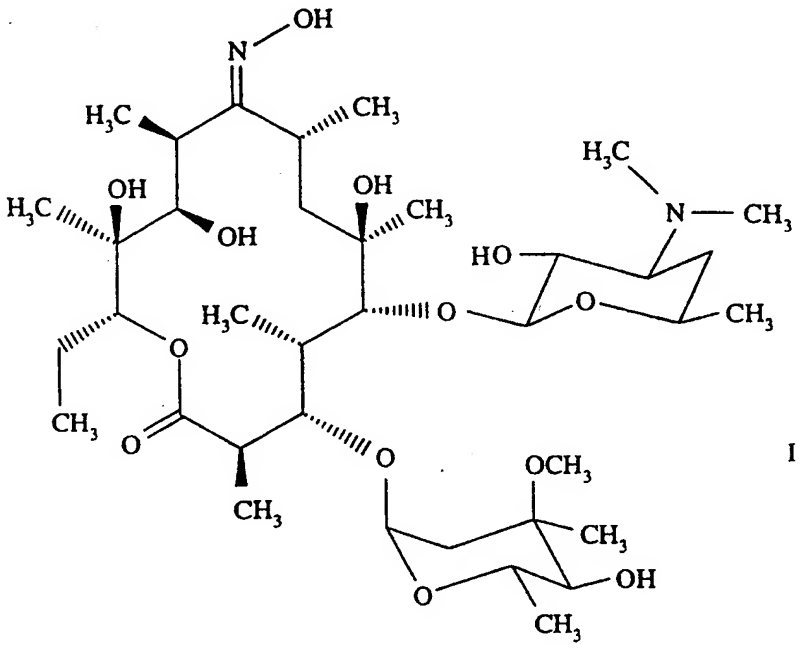
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

Intermediates in macrolide production

The present invention relates to intermediates useful in the synthesis of antibacterial macrolides, such as of the erythromycin type, for example erythromycin A type, e.g. roxithromycin, clarithromycin, azithromycin and similar compounds.

In US 3,478,014 there is described a compound of formula



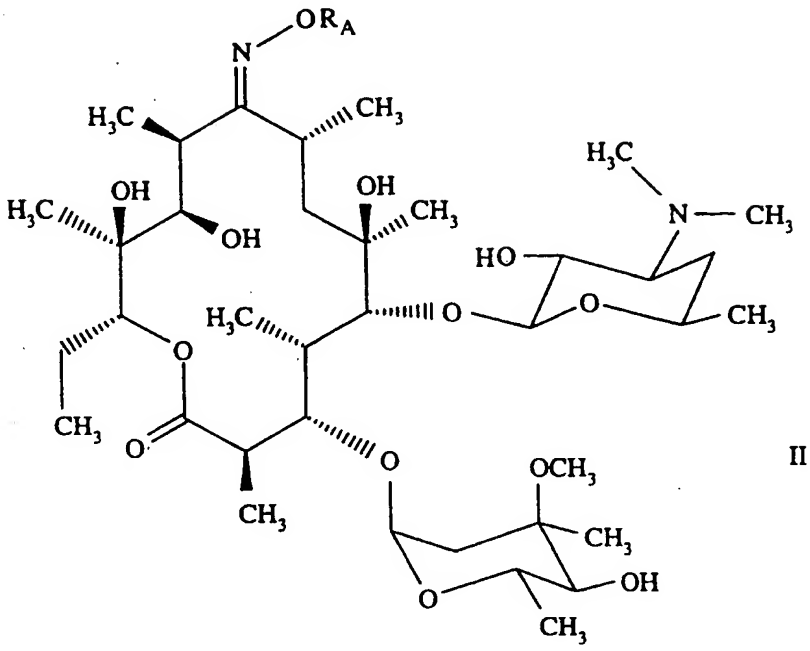
I

hereinafter designated as "erythromycin A oxime", which may be produced from erythomycin A which is a well known, e.g. antibacterial agent. Erythromycin A oxime may be useful in the production of antibacterial macrolides.

According to the present invention, novel intermediates, e.g. useful in the production of antibacterial macrolides have surprisingly been found, which may improve e.g. the production process of antibacterial macrolides, e.g. roxithromycin, azithromycin and clarithromycin.

In one aspect the present invention provides erythromycin A oxime, e.g. of formula I, wherein the hydroxyl group of the oxime group is in reacted form resulting from reaction with a strong organic base or with a silylation agent.

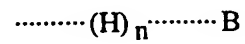
In another aspect the present invention provides a compound of formula



II

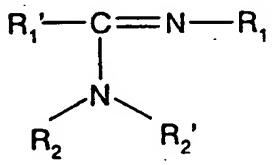
wherein R_A denotes

a silyl group; or a group of formula



wherein

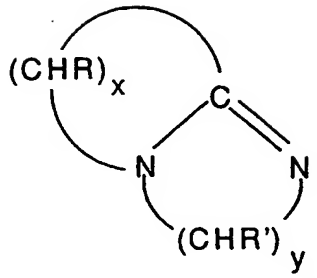
(i) n = 1 and B is a compound of formula



III

wherein R_1, R_1', R_2 and R_2' independently of each other denote hydrogen or an aliphatic or aromatic group; or R_1 and R_1' independently of each other denote an aliphatic or aromatic group and R_2 and R_2' together with the nitrogen atom denote a ring or ring system,

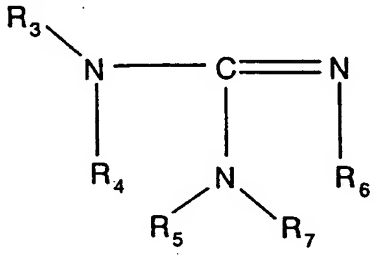
(ii) n = 1 and B is a compound of formula



IV

wherein R and R' independently of each other denote hydrogen or an aliphatic or aromatic group; x denotes 3, 4, or 5 and y denotes 2, 3 or 4;

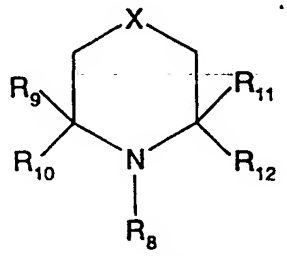
(iii) n = 1 and B is a compound of formula



V

wherein R_3, R_4,R_5, R_6 and R_7 denote independently of each other hydrogen or an aliphatic or aromatic group;
or R_3 is as defined above; and either R_4 and R_5 denote together (C_{1-4})alkylidene and R_6 and R_7 independently of each other denote hydrogen or an aliphatic or aromatic group; or R_4 and R_5 denote together (C_{1-4})alkylidene and R_6 and R_7 denote together (C_{1-4})alkylidene; or R_6 and R_7 denote together (C_{1-4})alkylidene and R_4 and R_5 independently of each other denote hydrogen or an aliphatic or aromatic group;

(iv) n = 1 and B is a compound of formula



VI

wherein R_8, R_9, R_{10}, R_{11} and R_{12} independently of each other denote hydrogen or an aliphatic or aromatic group, and X denotes CH_2, NH, O or S;

(v) n = 0 and B is a group of formula.

$$Z^{+}R_{13}R_{14}R_{15}R_{16} \qquad VII$$

wherein Z denotes nitrogen and R_{13}, R_{14}, R_{15}, and R_{16} independently of each other denote an aliphatic or aromatic group.

Erythromycin A, e.g. a compound of formula I, wherein the hydroxyl group of the oxime group is in reacted form resulting from reaction with a strong organic base is designated hereinafter as "Erythromycin A oxime in the form of an oximate with a strong organic base" or "An oximate according to the present invention" and includes a compound of formula II wherein R_A denotes a a group of formula

$$\cdots\cdots\cdots(H)_n\cdots\cdots\cdots B$$

wherein n and B are as defined above. The formation of erythromycin A oxime in the form of an oximate with a strong organic base may be determined, e.g. by mass spectroscopy, e.g. with electrospray as ionizing technique. The presence of the molecular peak of an oximate of erythromycin A oxime under such conditions may be evidence for oximate formation of erythrymycin A oxime with a strong organic base.

In another aspect, the present invention provides an oximate according to the present invention, e.g. a compound of formula II, wherein R, R', R_1, R_1', R_2, R_2', R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are as defined above, which shows a molecular peak of an oximate of erythromycin A oxime of formula I with a strong organic base in mass spectroscopy determination.

Amidine-type strong organic bases, e.g. compounds of formulae III and IV are e.g. commercially available, such as 1,5-diazabicyclo(4,3,0)non-5-ene (DBN) and 1,8-diazabicyclo(5,4,0)undec-7-ene (DBU); or may be easily produced, e.g. as appropriate, e.g. as conventional, for example by known, e.g. analogous methods, e.g. as described in Synthesis, 591 (1972) which is introduced herein by reference. Preferred compounds include DBN and DBU, e.g. DBU.

Guanidine-type strong organic bases, e.g. compounds of formula V, may be linear, e.g. R_3, R_4,R_5, R_6 and R_7 denote independently of each other hydrogen or an aliphatic or aromatic group; or cyclic, such as bicyclic, e.g. R_3 is as defined above; and either R_4 and R_5 denote together (C_{1-4})alkylidene and R_6 and R_7 independently of each other denote hydrogen or an

aliphatic or aromatic group; or R_4 and R_5 denote together (C_{1-4})alkylidene and R_6 and R_7 denote together (C_{1-4})alkylidene; or R_6 and R_7 denote together (C_{1-4})alkylidene and R_4 and R_5 independently of each other denote hydrogen or an aliphatic or aromatic group. Linear guanidines include e.g. tetramethylguanidine, pentamethylguanidine, tetraethylguanidine, tetramethylethylguanidine and tetramethylbenzylguanidine. Suitable cyclic and bicyclic guanidines include e.g. 1,5,7-triazabicyclo-(4,4,0)-dec-5-ene, and 7-methyl, 7-ethyl, 7-benzyl and 7-phenyl derivatives thereof. Preferred compounds of formula V include e.g. 1,1,3,3-tetramethylguanidine. Compounds of formula V are e.g. commercially available or may be easily produced, e.g. as appropriate, e.g. as conventional, for example by known, e.g. analogous methods described in prior art, e.g. in Synthetic Communications, 13, 67, (1983) which is introduced herein by reference.

Substituted piperidines, piperazines, morpholines and thiomorpholines, e.g. compounds of formula VI are known as strong organic alkyl bases. Compounds of formula VI are e.g. commercially available or may be easily produced, e.g. as appropriate, e.g. as conventional, for example by known, e.g. analogous, methods. Preferred compounds of formula VI include e.g. 2,2,6,6- tetramethylpiperidine and 1,2,2,6,6-pentamethylpiperidine.

Ammonium group type strong organic bases, e.g. of formula VII include beside the cation as defined in formula VII an appropriate anion, e.g. an hydroxide or halogenide, such as chloride, bromide. Compounds of formula VII including an appropriate anion are e.g. commercially available or may be easily produced, e.g. as appropriate, e.g. as conventional, for example by known, e.g. analogous, methods. Preferred compounds of formula VII include e.g. tetramethylammonium, tetraethylammonium, tetrabutylammonium and cetyltrimethyl-ammonium hydroxide and halogenide, e.g. chloride, bromide.

An oximate according to the present invention, e.g. of formula II, may have the following advantages compared with erythromycin A oxime:

- the oximate group may represent an "activated form" in an oximate according to the present invention, e.g. in the oximino group in position 9 of the ring system; and may have increased reactivity in comparison with erythromycin A oxime; e.g. in O-substitution of the oximino group in position 9 of the ring system; which may thus be performed under mild conditions and may avoid, e.g. degrading, side reactions;
- an oximate according to the present invention may show increased regioselectivity in comparison with erythromycin A oxime; e.g. in O-substitution of the oximino group in position 9 of the ring system; e.g. side reactions of free hydroxy groups in erythromycin A

oxime during O-substitution of the oximino group in position 9 of the ring system may be avoided;

- increased reactivity and regioselectivity of the oximate according to the present invention may result in higher yields in subsequent reactions in comparison with erythromycin A oxime;
- an oximate according to the present invention produced from erythromycin A oxime may have the same E- or Z-configuration as erythromycin A oxime used as starting material; e.g. the production of an oximate according to the present invention from erythromycin A oxime may be carried out without isomerisation reactions.

An oximate according to the present invention may be produced as follows:
A strong organic base, e.g. as described in the meaning of B in a compound of formula II above, and, in case that B means a cation of formula VII, a cation of formula VII with an appropriate anion, e.g. a hydroxide or halogenide, may be reacted with erythromycin A oxime;

- at appropriate reaction temperatures, including e.g. a range of ca. -50° C and the reflux temperature of a solvent (system) used, such as from -10° C to 40° C, and e.g. more than 40°C; and
- under appropriate pressure, e.g. under atmospheric pressure, and under a pressure which is above or below atmospheric pressure; and
- e.g. in a solvent or in a solvent system, e.g. in a mixture of solvents.

Appropiate solvents include halogenated solvents, such as halogenated aliphatic and aromatic, hydrocarbons, e.g. halogenated alkanes, e.g. dichloromethane; ketones such as dialkylketones, e.g. acetone; alkyl esters such as acetic acid esters, e.g. ethyl acetate and isopropyl acetate; hydrocarbons, such as aliphatic (alkyl) and aromatic (aryl) solvents, e.g. toluene; ethers such as cyclic, e.g. alkyl, ethers, having e.g. 4 to 8, e.g. 5 to 6 ring members, such as tetrahydrofurane; amides, e.g. alkyl amides, such as formic and acetic acid amides, e.g. formamide, N,N-dimethylformamide, N,N-dimethylacetamide and N-methylacetamide; preferably halogenated hydrocarbons, ketones and cyclic ethers, and mixtures of solvents e.g. comprising individual solvents as described above. The solvent system may include water, e.g. a small amount of water.
The amount of a strong organic base is not critical; if per equivalent erythromycin A oxime an amount of a strong organic base which is below one equivalent is used, a mixture of an oximate according to the present invention and of erythromycin A oxime may be obtained; if

per equivalent erythromycin A oxime an amount of a strong organic base which is one equivalent and more is used, an oximate according to the present invention may be obtained. An appropriate amount includes e.g. 1 to 20, such as 1 to 5, e.g. 1 to 3 equivalents of a strong organic base per equivalent erythromycin A oxime.

An oximate according to the present invention may be obained, e.g. in the form of an e.g. stable, solid, e.g. crystalline, precipitate, e.g. if appropriate, after removal of at least part of the solvent (system), e.g. by distillation or evaporation, e.g. in the presence of an anti-solvent. Precipitation and isolation of an oximate according to the present invention may be carried out as appropriate, e.g. as conventional in the precipitation and isolation of a compound from a reaction mixture, for example by known, e.g. analogous methods, such as solvent (system) evaporation, filtration, centrifugation.

Characterisation of an oximate according to the present invention may be carried out by IR, NMR and mass spectroscopy determination.

An oximate according to the present invention, such as of formua II, may exist as E-isomer, Z-isomer and mixtures of an E-isomer and an Z-isomer. An oximate according to the present invention produced according to the present invention may have the same E- or Z-configuration as erythromycin A oxime used as starting material; and undesired isomerisation reactions may be avoided.

In another aspect the present invention provides a process for the production of erythromycin A oxime, e.g. of formula I, in the form of an oximate with a strong organic base, such as of formua II, comprising reacting erythromycin A oxime with a strong organic base, e.g. of formulae III, IV,V and VI; and VII in the form of a cation of formula VII with an appropriate anion, such as a hydroxide or halogenide; and, if desired, isolating erythromycin A oxime, e.g. of formula I, in the form of an oximate, such as of formua II.

If not otherwise defined herein alkyl includes (C_{1-22})alkyl, e.g. (C_{1-8})alkyl, such as (C_{1-6})alkyl, for example (C_{1-4})alkyl; aryl includes (C_{5-18})aryl, such as C($_{o-12}$)aryl, preferably phenyl, napthyl. An aliphatic group includes e.g. alkyl, cycloylkyl, alkenyl and alkinyl; preferably alkyl. Alkenyl and alkinyl include e.g. (C_{2-22})alkenyl and alkinyl, e.g. (C_{2-8})alkenyl and alkinyl, such as (C_{2-6})alkenyl and alkinyl, for example (C_{2-4})alkenyl and alkinyl. Cycloalkyl includes (C_{3-8})cycloalkyl, such as (C_{4-7})cycloalkyl, e.g. (C_{5-6})cycloalkyl. An aromatic group includes aryl. A silyl group includes a silyl protecting group, e.g. a conventional silyl protecting group, such as a trialkylsilyl group, for example the trimethylsilyl group.

A ring includes e.g. an aliphatic and an aromatic ring having 4 to 8, e.g. 5 to 6 ring members; ring members include carbon atom based ring members and heteroatoms; e.g. up to 3 heteroatoms; e.g. selected from N, O, S; a ring system includes more than one ring, e.g. bicyclic or tricyclic rings. Any group defined herein may be unsubstituted or substituted, e.g. by groups which are inert under relevant reaction conditions.

An oximate according to the present invention may be useful e.g. in the production of intermediates, which may e.g. be useful in the production of macrolides, such as of the erythromycin type, for example erythromycin A type,
e.g. such as described in EP 33255, which is introduced herein by reference, e.g. in the production of roxithromycin; and
e.g. such as described in US 4,328,334, which is introduced herein by reference, e.g. in the production of azithromycin; and
e.g. such as described in EP 158467 and EP 272110 , which is introduced herein by reference, e.g. in the production of clarithromycin.
Reactions of erythromycin A oxime e.g. as described in the above cited references EP 33255, US 4,328,334, EP 158467 and EP 272110, and e.g. similar reactions of erythromycin A oxime, which e.g. may result in a compound described in the above cited references, may be carried out with an oximate according to the present invention, such as of formua II;
including e.g. O-alkylation, O-silylation, O-sulphonylation and O-acylation of the oximino group in position 9 of the ring system. An oximate according to the present invention may be used in isolated form; or an oximate according to the present invention may be formed "in situ" and used in subsequent reactions; e.g. without isolation of an oximate according to the present invention. Subsequent reaction of an oximate according to the present invention may be carried out as appropriate, e.g. as conventional, e.g. by reaction of an oximate according to the present invention with an appropriate alkylating, silylating, sulphonylating or acylating agent; e.g. in an appropriate, e.g. conventional solvent (system), at appropriate, e.g. conventional temperatures.
E.g. an O-alkylated erythromycin A oxime, such as roxythromycin may be produced by alkylation of an oximate according to the present invention, with an, e.g. conventional, alkylation agent; e.g. a compound of formula

Alk-L

wherein Alk denote an alkyl group and L denotes a leaving group, e.g. halogen, such as chloride, bromide, iodide, preferably chloride.

Alk includes alkyl which is interrupted by heteroatoms, e.g. oxygen, e.g. one or more, e.g. 2, such as alkoxyalkoxyalkyl, e.g. methoxyethoxymethyl; the oximate being e.g. produced in situ in the reaction mixture, or being an isolated oximate; e.g. in the presence of a solvent (system), e.g. as described above for the production of an oximate of the present invention.

In another aspect the present invention provides a process for the production of an O-alkylated erythromycin A oxime, e.g. roxythromycin, comprising reacting a compound of formula II, wherein R_A denotes a group of formula

$$\cdots\cdots(H)_n\cdots\cdots B$$

wherein n an B are as defined above with a compound of formula

Alk-L

wherein Alk denote an alkyl group, e.g. methoxyethoxymethyl, and L denotes a leaving group, e.g. halogen, such as chloride, bromide, iodide, preferably chloride.

E.g. an O-sulphonylated erythromycin A oxime, such as (E)-9-[O-(p(toluenesulphonyl)oxime of erythromycin A may be produced by sulphonylation of an oximate according to the present invention; the oximate being e.g. produced in situ in the reaction mixture, or being an isolated oximate; with an, e.g. conventional, sulphonylating agent, e.g. p-toluenesulphonyl chloride; in the presence of a solvent (system) , e.g. as described above for the production of an oximate of the present invention, e.g. acetone.

E.g. an O-acylated erythromycin A oxime, such as (E)-9-[O-(phenylacetyl)oxime of erythromycin A may be produced by acylation of an oximate according to the present invention; the oximate being e.g. produced in situ in the reaction mixture, or being an isolated oximate; with an, e.g. conventional, acylation agent, e.g. phenacetyl chloride; in the presence of a solvent (system) , e.g. as described above for the production of an oximate of the present invention, e.g. acetone.

E.g. an O-silylated erythromycin A oxime includes a compound of formula II wherein R_A denotes a silyl group, e.g. of formula $SiR'_4R'_5R'_6$, wherein R'_4, R'_5 and R'_6 independently of each other denote hydrogen, alkyl, alkenyl, cycloalkyl, aryl; preferably alkyl, e.g. (C_{1-8})alkyl, such as (C_{1-6})alkyl, e.g. (C_{1-4})alkyl, such as methyl, ethyl, iso-propyl, butyl. Erythromycin A oxime wherein the hydroxy group in the hydroxyimino group is silylated is new.

In another aspect the present invention provides erythromycin A oxime wherein the hydroxy group in the hydroxyimino group is silylated.

A process for the production of a compound of formula II wherein R_A denotes a silyl group may be carried out as follöws:
As a starting material erythromycin A oxime in the form of an oximate with a strong organic base according to the present invention, preferably an DBU or TMG oximate, e.g. in a solvent or solvent system, e.g. chlorinated solvents such as dichloromethane; ketones such as acetone; alkyl esters such as ethyl acetate, isopropyl acetate or n-butyl acetate; hydrocarbons; ethers; polar aprotic solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide; and a mixture of one or more solvents, e.g. as described above may be reacted with a silylating agent, e.g. which is conventional for the silylation of hydroxyl groups, including silanes such as trialkylmonochlorosilanes, e.g. trimethylchlorosilane, dialkyldichlorosilanes, silylated amides, such as bisilylacetamides, e.g. N-O-bis(trimethylsilyl)acetamide, silylated ureas such as bisilylurea, e.g. N,N-bis(trimethylsilyl)urea, silylated amines, e.g. hexamethyldisilazane, silylated organic bases, such as silylated imidazoles, e.g. trimethylsilylimidazole; and mixtures of silylated agents, e.g. as described above, preferably monochlorosilanes, e.g. trimethylchlorosilane, t-butyldimethylchlorosilane and triisopropylchlorosilane; at an appropriate reaction temperature, e.g. between -50°C, e.g. -10°C and the refluxing temperature of the solvent system used. Per equivalent of an oximate according to the present invention, e.g. ca., one to, e.g. ca., 1.5, such as 1 to 1.1 equivalents of a silylation agent may conveniently be used. A compound of formula II wherein R_A denotes a silyl group may be obtained and may precipitate; e.g. after removal of solvent; and if desired, may be isolated, e.g. as conventional.

In another aspect the present invention provides a process for the production of erythromycin A oxime wherein the hydroxy group in the hydroxyimino group is silylated comprising silylating a compound of formula II wherein R_A denotes a group of formula

$$\cdots\cdots (H)_n \cdots\cdots B$$

wherein n and B are as defined above.

Erythromycin A oxime wherein the hydroxy group in the hydroxyimino group is silylated, e.g. protected by silyl, may be useful as an intermediate in the production of macrolides, e.g.

in reactions in other positions of the ring system than in position 9 of the ring system, e.g. in reactions which require the hydroxy group of the oxime in protected form.

Erythromycin A oxime wherein the hydroxy group in the hydroxyimino group is silylated may be further silylated in position 2' and 4" of the ring system.

Thus, in another aspect the present invention provides a process for the production of a compound of formula II wherein R_A denotes silyl and wherein the hydroxy groups in position 2' and 4" of the ring system are silylated, e.g. by a group $SiR'_4R'_5R'_6$ wherein R'_4, R'_5 and R'_6 are as defined above, comprising reacting a compound of formula II, wherein R_A denotes a a silyl group with a silylating agent.

Silylation may be carried out as appropriate, e.g. as conventional, e.g. as described above for the silylation of the 9-hydroxyimino group; preferably in the presence of a silylated imidazole, e.g. a tri(C_{1-4})alkylsilylimidazole, such as 1-(trimethylsilyl)imidazole, and e.g. in the presence of a silane, e.g. a trialkylmonochlorosilane, such as trimethylchlorosilane as a silylation agent. The amount of silylation agent is not critical; conveniently at least 2 equivalents and more, e.g. up to 5 equivalents silylation agent per equivalent of a compound of formula II, wherein R_A denotes a silyl group may be used. In a preferred embodiment silylation of the hydroxyl groups in position 9, 2' and 4" of the ring system may be carried out in an one pot reaction starting from an erythromycin A oximate according to the present invention.

In still another aspect the present invention provides a process for the production of 6-O-alkyl erythromycins A comprising the steps

i) producing a compound of formula II wherein R_A denotes a silyl group;

ii) reacting a compound obtained in step i) with a silylating agent to obtain a compound of formula II wherein R_A denotes a silyl group and wherein the hydroxyl groups in position 2' and 4" are silylated;

iii) treating a compound obtained in step ii) with an alkylating agent to obtain a compound of formula II wherein R_A denotes a silyl group and wherein the hydroxyl groups in position 2' and 4" are silylated and wherein the hydroxyl group in position 6 is alkylated; and

iv) removing the silyl groups from and deoximating a compound obtained in step iii) to obtain erythromycin A wherein the hydroxy group in position 6 of the ring system is alkylated; e.g. clarithromycin.

Step iii) may be carried out as in conventional alkylation, e.g.in the presence of a base and an alkylating reagent; e.g. for methylation analogously as described in T.W. Greene et alt.: "Protective Groups in Organic Synthesis", second edition, 1991, pages 14-16, John Wiley & Sons Inc.. Preferred alkylating agents include methyl bromide, -iodide, dimethyl sulphate, methyl p-toluenesulphonate, methyl methanesulphonate, ethyl bromide, ethyl iodide , diethyl sulphate, n-propyl bromides and -iodides. Preferred solvents include polar solvents, such as tetrahydrofuran, ethyl acetate or acetone; polar aprotic solvents such as N,N-dimethyl-formamide, dimethylsulfoxide, N-methyl-2-pyrrolidone and a mixture of two or more solvents as described. A preferred base includes sodium and potassium hydroxide, sodium and potassium hydride, lithium diisopropylamide, alkaline alkoxides, such as sodium methoxide and amines such as triethylamine or diisopropylethylamine; or a mixture of two or more bases as described. Preferably alkylation may be carried out at temperatures between -40 and 40°C, preferably between -10 and 30°C.

Silyl groups from the hydroxy groups in 2', 4'' and 9 of the ring system may e.g. be removed under acidic conditions or in the presence of fluoride ions, e.g. by a method as conventional, e.g. analogously as described in T.W. Greene et alt.: "Protective Groups in Organic Synthesis", second edition, 1991, pages 68-87, John Wiley & Sons Inc..

Deoximation of the oxime group to obtain a carbonyl group may be carried out as conventional, e.g. as described in T.W. Greene et al., "Protective Groups in Organic Synthesis", second edition, 1991, pages 68-87, John Wiley & Sons Inc or in J. March: "Advanced Organic Chemistry", fourth edition, 1992, pages 884-885.

Removal of the silyl groups and deoximation under acidic conditions may be carried out simultanously.

E.g. erythromycin A oximes wherein the hydroxy group of the oxime is alkylated, e.g. roxythromycin, and wherein the hydroxy group of the oxime is acylated, silylated or sulphonylated, e.g. obtained according to the present invention, is a useful intermediate e.g. in the production of clarithromycin. Conversation of an erythromycin wherein the hydroxy group of the oxime is alkylated, e.g. roxythromycin, into clarithromycin is new.

In another aspect the present invention provides a process for the production of clarithromycin comprising the steps

i) silylating the hydroxy groups in position 2' and 4'' in the ring system of an erythromycin A oxime wherein the hydroxy group of the oxime is alkylated, e.g. roxythromycin, e.g. which is obtained by reacting a compound of formula II, wherein R_A denotes a group of formula

$$\cdots\cdots(H)_n\cdots\cdots B$$

wherein n an B are as defined above with a compound of formula

Alk-L

e.g. a compound of formula

$CH_3OC_2H_5OCH_2$-L

wherein Alk denotes an alkyl group and L denotes a leaving group,

ii) methylating the hydroxy group in position 6 of the ring system in a compound obtained in step i) to obtain erythromycin A oxime wherein the hydroxy group of the oxime is alkylated, e.g. roxythromycin and wherein the hydroxyl groups in position 2' and 4'' are silylated and wherein the hydroxyl group in position 6 is methylated; and

iii) removing the silyl groups from and deoximating a compound obtained in step ii) to obtain clarithromycin; e.g. and isolating clarthromycin, e.g. in the form of a salt and/or in the form of a solvate from a reacction mixture.

A process according to the present invention may be carried out as follows:
Erythromycin A oximes wherein the hydroxy group of the oxime is alkylated, e.g. roxythromycin may be produced e.g. according to an appropriate process, e.g. as conventional, or, preferably, according to the present invention, e.g. as described above. Silylation of the hydroxy groups in positions 2' and 4'' of the ring system may be carried out e.g. analogously as described above in the production of a compound of formula II, wherein R_A denotes silyl and wherein the hydroxy groups in position 2' and 4'' of the ring system are silylated and using an erythromycin A oxime wherein the hydroxy group of the oxime is alkylated, e.g. roxythromycin instead of a compound of formula II, wherein R_A denotes silyl as a starting material. Methylation of the hydroxy group in position 6 of the ring system in an erythromycin A oxime wherein the hydroxy group of the oxime is alkylated, e.g. roxythromycin, and wherein the hydroxy groups in positions 2' and 4'' of the ring system are silylated may be carried out analogously as described above in the production of clarithromycin but using an erythromycin A oxime wherein the hydroxy group of the oxime is alkylated, e.g. roxythromycin and wherein the hydroxy groups in position 2' and 4'' of the

ring system are silylated instead of a compound of formula II, wherein R_A denotes a silyl group and wherein the hydroxy groups in position 2' and 4'' of the ring system are silylated, as a starting material. Removal of the silyl groups and deoximation of erythromycin A oximes wherein the hydroxy group of the oxime is alkylated, e.g. roxythromycin, and wherein the hydroxy groups in position 2' and 4'' of the ring system are silylated and wherein the hydroxyl group in position 6 of the ring system is methylated may be carried out e.g. analogously as described above in the production of clarithromycin but using an erythromycin A oxime wherein the hydroxy group of the oxime is alkylated, e.g. roxythromycin, and wherein the hydroxy groups in position 2' and 4'' of the ring system are silylated and wherein the hydroxyl group in position 6 of the ring system is methylated instead of a compound of formula II, wherein R_A denotes a silyl group and wherein the hydroxy groups in position 2' and 4'' of the ring system are silylated and wherein the hydroxyl group in position 6 is methylated, as a starting material.

In another aspect the invention provides the use of erythromycin A oxime wherein the hydroxyl group of the oxime group is in reacted form resulting from reaction with a strong organic base or with a silylation agent, such as of formua II, as an intermediate, e.g. in reactions of the hydroxyl group of the oxime group, such as e.g. O-alkylation, O-silylation, O-sulphonylation, O-acylation; useful e.g. in the production of macrolides of the erythromycin type, for example erythromycin A type, e.g. in the production of e.g. roxithromycin, e.g. clarithromycin, e.g. azithromycin and e.g. similar compounds.

The following non limitative examples illustrate the present invention.Temperatures are given in degree Celsius and are uncorrected.

Erythromycin A oxime is a compound of formula I.

Characterization of erythromycin A oxime in the form of an oximate with a strong organic base is carried out by IR (data given describe the most characteristic absorption bands), ^{1}H-NMR and mass spectroscopy (MS).

Mass spectroscopy data (MS) are determined by use of electrospray as ionizing technique (ESP +), which allows determination of the molecular peak of an erythromycin A oxime in the form of an oximate.

^{1}H-NMR determination, shown in Table 1, shows a molar ratio of about 1:1 between the strong organic base and erythromycin A oxime in an erythromycin A oxime in the form of an oximate.

DBU: 1,8-diazabicyclo (5,4,0) undec-7-ene

TMG: 1,1,3,3,-tetramethylguanidine

PMP: 1,2,2,6,6-pentamethylpiperidine

TMA: tetramethylammonium

DBU oximate: Erythromycin A oxime in the form of an oximate with DBU

TMG oximate: Erythromycin A oxime in the form of an oximate with TMG

PMP oximate: Erythromycin A oxime in the form of an oximate with PMP

TMA oximate: Erythromycin A oxime in the form of an oximate with TMA

MEM-Cl: Methoxyethoxymethyl chloride

C (I) in Table 1: Number of C-atom shown in the ring system of formula I(C)

OXIME (in Table 1): Erythromycin A oxime of formula I

MS-FAB: Mass spectra

THF: tetrahydrofurane

DMF: dimethylformamide

DMSO: dimethylsulphoxide

Example 1

DBU oximate

1.5 g of erythromycin A oxime are suspended in 8 ml of methylenechloride at 20°. 0.3 ml of DBU are added and the mixture is stirred for ca. 1 hour at room temperature. The reaction mixture is concentrated under vacuum. DBU oximate precipates as a white, crystalline solid and is filtrated off.

Yield: 1.8 g (100 % of theory); MS (ESP + ; F = 50): m/z = 902 (MH^+); IR (KBr, cm^{-1}): 3600-3450, 1736, 1640, 1615; ^{1}HNMR data shown in TABLE 1 below.

Example 2

According to the method of example 1, but using 8 ml of acetone instead of methylene chloride, 1.7 g (94 % of theory) of solid DBU oximate are obtained. Characterisation as in Example 1.

Example 3

TMG oximate

0.25 ml of TMG are added to a solution of 1.50 g of erythromycin A oxime in 10 ml of methylene chloride. The mixture is stirred at room temperature. After ca. 1 hour, the solvent is evaporated off. Solid TMG oximate is obtained.

Yield: 1.62 g (94 % of theory); MS (ESP + ; F = 50): m/z = 865 (MH^+); IR (KBr, cm^{-1}): 3600-3460, 1738, 1594, 1462; ^{1}HNMR data shown in TABLE 1 below.

Example 4

PMP oximate

1.5 g of erythromycin A oxime are suspended in 8 ml of methylenechloride at ca. 20°C. 0.36 ml of PMP are added and the mixture is stirred for ca. 1 hour at room temperature and concentrated under vacuum. Solid PMP oximate is obtained.

Yield: 1.81 g (100% of theory); MS (ESP + ; F = 50): m/z = 905 (MH^+); IR (KBr, cm^{-1}): 3600-3000, 1739, 1709, 1641, 1463; ^{1}HNMR data shown in TABLE 1 below.

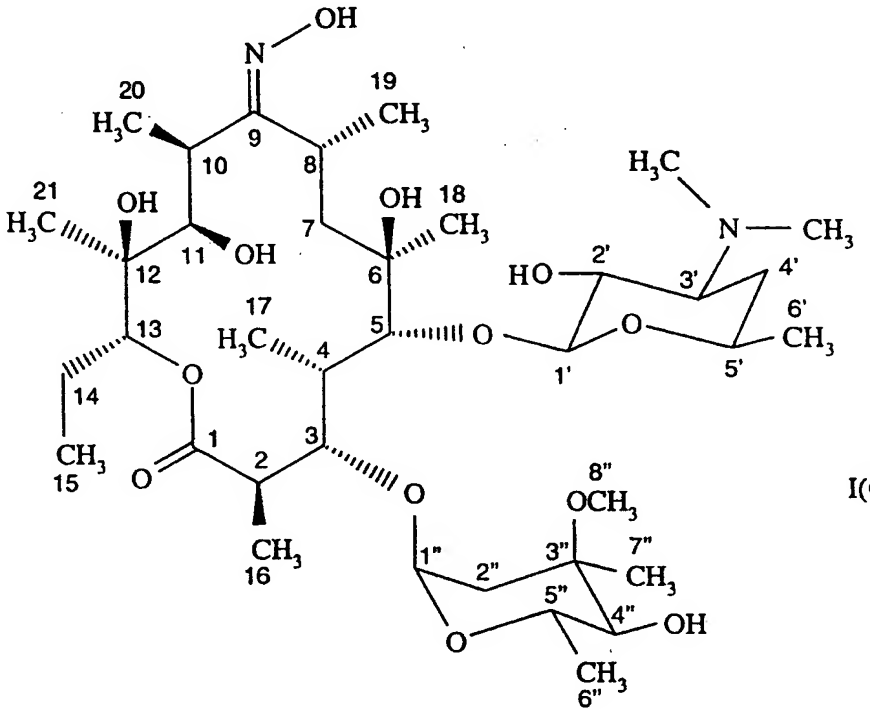
Example 5

TMA oximate

To a solution of 3.1 g of erythromycin A oxime in 15 ml of THF, cooled to ca. 0°, 747 mg of tetramethylammonium hydroxide in 15 ml of THF are added and the mixture is stirred for ca.

30 min at ca. 0°-5 °, dried over $MgSO_4$ and concentrated under vacuum. Solid TMA oximate is obtained.

Yield: 2.96 g (90% of theory); MS (ESP + ; F = 50): m/z = 823 (MH^+); IR (KBr, cm^{-1}): 3600-3075, 1727, 1645,1566, 1489, 1378; ^{1}HNMR data shown in TABLE 1 below.



I(C)

TABLE 1

C (I)	OXIME	DBU oximate	TMG oximate	PMP oximate	TMA oximate
1	175.6	174.8	174.9	175.0	175.8
2	44.7	44.5	44.6	44.6	44.6
3	80.1	79.8	80.0	80.0	79.0
4	38.9	38.6	38.7	38.8	38.9
5	83.3	82.9	83.1	83.2	82.0
6	75.2	75.0	75.1	75.2	75.1

C (I)	OXIME	DBU oximate	TMG oximate	PMP oximate	TMA oximate
7	37.7	37.7	37.8	37.7	37.7
8	25.3	25.3	25.3	25.3	25.5
9	171.4	169.7	170.3	171.0	168.5 (broad)
10	32.6	32.2	32.4	32.5	32.1
11	70.8	71.0	71.0	70.9	70.9
12	74.3	74.0	74.2	74.2	73.6
13	77.2	77.2	76.8	76.8	76.6
14	20.9	20.9	20.9	21.0	20.8
15	10.6	10.6	10.6	10.6	10.6
16	16.1	16.1	16.2	16.3	16.0
17	9.2	9.2	9.2	9.2	9.1
18	26.9	27.1	27.1	27.1	27.7
19	18.5	18.5	18.5	18.6	18.4
20	14.2	14.2	14.2	14.3	14.1
21	16.2	16.3	16.2	16.3	16.3
1'	103.0	102.7	102.8	102.9	102.3
2'	71.0	71.0	71.1	71.1	71.0
3'	65.3	65.2	65.3	65.4	65.4
4'	28.9	28.9	29.0	28.9	28.7
5'	68.7	68.5	68.6	68.7	68.5
6'	21.3	21.3	21.3	21.4	21.3
$N(CH_3)_2$	40.2	40.2	40.2	40.3	40.2
1"	96.3	96.1	96.2	96.2	95.9
2"	34.9	35.0	35.1	35.1	35.0
3"	72.6	72.6	72.6	72.6	72.6
4"	77.9	77.9	78.0	78.0	77.8
5"	65.4	65.3	65.3	65.4	65.4
6"	18.6	18.6	18.6	18.7	18.8
7"	21.4	21.4	21.4	21.5	21.4
8"	49.4	49.3	49.4	49.4	49.4
	DBU				

C (I)	OXIME	DBU oximate	TMG oximate	PMP oximate	TMA oximate
	161.4	162.7			
	52.8	52.9			
	48.3	48.3			
	44.3	42.3			
	37.4	35.5			
	29.8	29.5			
	28.5	28.1			
	26.0	25.2			
	22.5	21.7			
	TMG				
	169.0		167.6		
	39.4		39.2		
	PMP				
	53.7			54.0	
	41.2			40.9	
	28.5			28.5	
	26.3			26.2	
	17.9			17.8	
	TMA (chloride)				
	58.0				56.0
	(broad)				(broad)

In TABLE 1 C(I) corresponds to the position of the carbon atoms in the ring system of a compound of formula I(C). The numerical values are the ^{1}HNMR data values.

Example 6

Roxythromycin via alkylation of TMG oximate

0.86 g of TMG oximate, obtained as described in example 2 are dissolved in 5 ml of THF under nitrogen atmosphere. 0.23 ml of MEM-Cl and 0.13 ml of TMG are added. The reaction mixture is heated to ca. 40°C and is kept at this temperature for ca. 4 hours. HPLC determination shows a conversion of TMG oximate into roxithromycin of 80%.

Example 7

Roxythromycin via alkylation of TMG oximate

To a solution of 0.86 g of TMG oximate in 2 ml of toluene are added 0.05 g of tetrabutylammonium bromide, 2 ml of 10 % aqueous NaOH solution and 0.23 ml of MEM-Cl are added to the mixture and the reaction mixture is heated to 40° for ca. 2 hours. 0.11 ml of MEM-Cl and 1 ml of 10% aqueous NaOH solution are added and the mixture is heated to 40°c for ca. 1 hour. HPLC determination shows a conversion of TMG oximate into roxithromycin of 87%.

Example 8

Roxythromycin via alkylation of DBU oximate

To a suspension of 9.0 g of erythromycin A oxime in 24 ml of toluene, 1.8 mL of DBU are added and the mixture is stirred for ca. 1 hour at room temperature. DBU oximate is formed in situ. The reaction mixture is stirred for ca. 1 hour and 0.58 mg of tetrabutylammonium bromide, 24 ml of a 2N aqueous NaOH solution and 2.75 ml of MEM-Cl are added. The reaction mixture is heated to 40°, stirred for ca. 2 hours at this temperature and treated with 12 ml of a 2N aqueous NaOH solution and 1.4 ml of MEM-Cl. Stirring is continued for ca. 2 hours. HPLC determination shows a conversion of DBU oximate into roxythromycin of 76 %.

Example 9

Roxythromycin via alkylation of TMA oximate

To a suspension of 6.3 g of erythromycin A oxime in 30 ml acetone 5.7 ml of a 25 % w/w aqueous solution of tetramethyl ammonium hydroxide are added at ca. 0°-5°. The mixture is stirred for ca. 15 minutes at ca. 0°-5 °. Erythromycin A oxime in the form of an oximate with TMA is obtained in situ. 1.3 ml of MEM-Cl are added to the reaction mixture and the mixture is stirred for ca. 30 minutes at ca. 0°-5°. HPLC determination shows a conversion of TMA oximate into roxithromycin of 83%.

Example 10

(E)-9-[O-(phenylacetyl)oxime of erythromycin A via acylation of DBU oximate

A mixture of 3.15 g of erythromycin A oxime and 0.66 mL of DBU in 70 ml of acetone is stirred for ca. 1 hour at room temperature. DBU oximate is obtained in situ. The reaction mixture is cooled to ca. 0°-5 °, a solution of 0.6 ml of phenylacetyl chloride in 5 ml of acetone is added dropwise within ca. 10 minutes and the mixture obtained is stirred for ca. 1 hour at ca. 0°-5°. HPLC determination shows a conversion of DBU oximate into (E)-9-[O-(phenylacetyl)oxime of erythromycin A of 83 %. (E)-9-[O-(phenylacetyl)oxime of erythromycin A is isolated as a solid.

MS (FAB): 867 (M^+); IR (KBr, cm^{-1}): 3600-3300, 1735, 1648, 1588, 1496, 1458, 1379; ^{13}C NMR: d 168.6 ($PhCH_2COON=C9$), 166.2 ($PhCH_2COON=C9$), 133.1 ($PhCH_2COON=C9$), 129.3 ($PhCH_2COON=C9$), 128.6 ($PhCH_2COON=C9$), 127.2 ($PhCH_2COON=C9$), 54.3 ($PhCH_2COON=C9$)

Example 11

(E)-9-[O-(phenylacetyl)oxime of erythromycin A via acylation of PMP oximate

1.0 g of PMP oximate, obtained as described in example 4, is dissolved in 25 ml of acetone. The mixture obtained is cooled to ca. 0°-5°, 0.18 ml of phenylacetyl chloride, dissolved in 3 ml of acetone, are added and the mixture is stirred at ca. 0°-5° for ca. 1 hour. HPLC determination shows a conversion of PMP oximate into (E)-9-[O-(phenylacetyl)oxime of erythromycin A of 87 %. Isolation and characterisation as described in Example 10.

Example 12

(E)-9-[O-(phenylacetyl)oxime of erythromycin A via acylation of TMA oximate

2.41 g of TMA oximate, obtained as described in example 5, are dissolved in 50 ml of acetone, coooled to ca. 0°-5° and treated dropwise with a solution of 0.42 ml of phenylacetyl chloride in 5 ml of acetone. The reaction mixture is stirred at ca. 0°-5° for ca. 1 hour. HPLC determination shows a conversion of TMA oximate into (E)-9-[O-(phenylacetyl)oxime of erythromycin A of 92.1%. Isolation and characterisation as described in Example 10.

Example 13

(E)-9-[O-(p-toluensulphonyl)oxime of erythromycin A via sulphonylation of TMG oximate

To a solution of 3.11 g of erythromycin A oxime in 60 ml of acetone, 0.55 ml of TMG are added, the mixture is stirred at room temperature for ca. 1 hour and cooled to ca. 0°-5°.

0.55 ml of TMG and a solution of 1.68 g of p-toluensulfonyl chloride in 30 ml of acetone are added within ca. 30 minutes and the mixture is stirred at ca. 0°-5 ° for ca. 4 hours.
HPLC determination shows a conversion of TMG oximate into (E)-9-[O-(p-toluensulphonyl)oxime of erythromycin A of 90%.

Example 14

E)-9-[O-(p-toluensulphonyl)oxime of erythromycin A via sulphonylation of DBU oximate

A mixture of 3.11 g of erythromycin A oxime in 60 ml of acetone and 0.65 ml of DBU is stirred at room temperature for ca. 1 hour and cooled to ca. 0°-5°. 0.65 ml of DBU and a solution of 1.68 g of p-toluensulfonyl chloride in 30 ml of acetone are added to the reaction mixture within ca. 30 minutes, the mixture obtained is stirred at ca. 0°-5° for ca. 4 hours.
HPLC determination shows a conversion of DBU oximate into (E)-9-[O-(p-toluensulphonyl)oxime of erythromycin A of 73.8%.

Example 15

9-O-trimethylsilyl-erythromycin A-9-oxime

To a solution of 1.5 g of the TMG oximate of erythromycin A in 15 ml of methylenechloride, cooled at 0 °C, 0.22 ml of trimethylchlorosilane are added. The mixture is stirred for ca. 20 hours at room temperature and poured over water. The layers are separated and the aqueous layer is extracted with methylenechloride. The organic layer is washed with a saturated solution of $NaHCO_3$, dried over anhydrous sodium sulphate and concentrated to dryness under vacuum. 1.28 g of 9-O-trimethylsilyl-erythromycin A-9-oxime are obtained.
Yield: 91.6%of theory; MS (FAB +): m/z= 822 (M^+); IR (KBr, cm^{-1}): 3600-3350, 1738, 1613, 1462, 1380; ^{13}C-NMR ($CDCl_3$, 75.4 MHz): d 174.8 (C=N), -0.04 (Me_3SiON=)

Example 16

9-O-*tert*-butyldimethylsilyl-erythromycin A-9-oxime

Is carried out analogously as described in example 15 but using 283 mg of *tert*-butyldimethylchlorosilane instead of 0.22 ml of trimethylchlorosilane. 1.32 g of 9-O-*tert*-butyldimethylsilyl-erythromycin A-9-oxime are obtained.
Yield: 89.9% of theory; MS (FAB +): m/z= 864 (M^+); IR (KBr, cm^{-1}): 3600-3400, 1738, 1464, 1380; ^{13}C-NMR ($CDCl_3$, 75.4 MHz): d 174.9 (C=N), 25.8 ($\underline{Me}_3CSiMe_2$), -5.3 ($Me_3CSi\underline{Me}_2$)

Example 17

9-O-triisopropylsilyl-erytrhomycin A-9-oxime

Is carried out analogously as described in example 15 but using 0.37 ml of triisopropylchlorosilane instead of 0.22 ml of trimethylchlorosilane and stirring the mixture for ca. 60 hours instead of ca. 20 hours. at room temperature 1.43 g of 9-O-triisopropylsilyl-erytrhomycin A-9-oxime are obtained.

Yield: 91.2% of theory

MS (FAB +): m/z= 906 (M^+); IR (KBr, cm^{-1}):3600-3400, 1740, 1464, 1381

^{13}C-NMR ($CDCl_3$, 75.4 MHz): d 174.5 (C=N), 17.8 (Me_2CHSi), 11.7 (Me_2CHSi)

Example 18

2',4",9-O-tris(trimethylsilyl)-erythromycin A-9-oxime

To a solution obtained after ca. 20 hours of stirring as described in example 15, 0.35 ml of trimethylchlorosilane and 0.65 ml of 1-(trimethylsilyl)imidazole are added and the mixture is stirred at room temperature for ca. 1 hour. A precipitate formed is filtrated off. The filtrated solution is washed with a saturated solution of $NaHCO_3$, dried over anhydrous sodium sulphate and concentrated to dryness under vacuum. 1.42 g of 2',4",9-O-tris(trimethylsilyl)-erythromycin A-9-oxime are obtained

Yield: 85.0% of theory; MS (FAB +): m/z= 966 (M^+); ^{13}C-NMR ($CDCl_3$, 75.4 MHz): d 175.3 (C=N), 80.9 (4"), 74.3 (2'), 1.0 (Me_3Si), 0.9 (Me_3Si), -0.8 (Me_3SiON=)

Analogously as described in example 18 but using the corresponding silylation agent the following compounds are prepared:

2',4"-O-bis(trimethylsilyl)-9-O-*tert*-butyldimethylsilyl-erythromycin A-9-oxime

Yield: 85.0%of theory; MS (FAB +): m/z= 1008 (M^+);

^{13}C-NMR ($CDCl_3$, 75.4 MHz): d 174.8 (C=N), 80.9 (4"), 74.3 (2'), 25.8 (Me_3CSiMe_2), 1.0 (Me_3Si), 0.9 (Me_3Si), -5.3 (Me_3CSiMe_2)

2',4"-O-bis(trimethylsilyl)-9-O-triisopropylsilyl-erytrhomycin A-9-oxime

Yield: 84.2%of theory; MS (FAB +): m/z= 1050 (M^+):

^{13}C-NMR ($CDCl_3$, 75.4 MHz): d 175.2 (C=N), 80.7 (4"), 74.2 (2'), 17.9 (Me_2CHSi), 11.7 (Me_2CHSi), 1.0 (Me_3Si), 0.9 (Me_3Si)

Example 19

a. Methylation of 2',4",9-O-tris(trimethylsilyl)-erythromycin A-9-oxime

To a solution of 3.9 g of 2',4",9-O-tris(trimethylsilyl)-erythromycin A-9-oxime in 50 ml of THF, cooled at 0 °C, 3.5 ml of sodium methoxide (30% in methanol) are added. The mixture obtained is kept under stirring at ca. 0 °C for ca. 30 minutes and 1.05 ml of methyl iodide are added. After ca. 2 hours at ca. 0 °C, 25 ml of water and 50 ml of methylenechloride are added. The phases are separated and the organic phase is washed with a saturated solution of $NaHCO_3$, dried over anhydrous magnesium sulphate and concentrated to dryness under vacuum. 4.02 g of 2',4",9-O-tris(trimethylsilyl)-erythromycin A-9-oxime wherein the hydroxy group in position 6 of the ring system is methylated in the form of a white solid is obtained, confirmed by MS and NMR spectra characerization data.

b. Methylation of 2',4"-O-bis(trimethylsilyl)-9-O-*tert*-butyldimethylsilyl-erythromycin A-9-oxime

Analogously as described in example 19 a., but starting from 2',4"-O-bis(trimethylsilyl)-9-O-*tert*-butyldimethylsilyl-erythromycin A-9-oxime and using as a solvent DMF instead of THF and as a base sodium hydride (80%) instead of sodium methoxide and ethyl acetate instead of methylenechloride 2',4",9-O-tris(trimethylsilyl)-erythromycin A-9-oxime wherein the hydroxy group in position 6 of the ring system is methylated in the form of a white solid is obtained, confirmed by MS and NMR spectra characerization data.

c. Methylation of 2',4"-O-bis(trimethylsilyl)-9-O-triisopropylsilyl-erythromycin A-9-oxime

Analogously as described in example 19 a., but starting from 2',4"-O-bis(trimethylsilyl)-9-O-triisopropylsilyl-erythromycin A-9-oxime and using as a solvent DMSO/THF (1:1) instead of THF and as a base powdered KOH and triethylamine instead of sodium methoxide and ethyl acetate instead of methylenechloride 2',4"-O-bis(trimethylsilyl)-9-O-triisopropylsilyl-erythromycin A-9-oxime wherein the hydroxy group in position 6 of the ring system is methylated in the form of a white solid is obtained, confirmed by MS and NMR spectra characerization data.

Example 20

6-O-methyl-erythromycin A-9-oxime

A crude solid obtained according to example 19 is dissolved in a mixture of ethanol and water (1:1). The solution is acidified by addition of formic acid and the mixture is kept at room temperature. After stirring for ca. 3-5 hours, 6-O-methyl-erythromycin A-9-oxime is obtained.

MS (FAB +): m/z= 763 (M^+); IR (KBr, cm^{-1}): 3600-3350, 1738, 1613, 1462, 1380
^{13}C-NMR ($CDCl_3$, 75.4 MHz): d 170.4 (C=N), 51.1 (6-O-Me)

Example 21

6-O-Methyl-erythromycin A (clarithromycin)

To a solution of 264 mg of 6-O-methyl-erythromycin A-9-oxime obtained according to example 20, in 4 ml of ethanol/water (1:1), 146 mg of sodium hydrogen sulfite and 33 ml of formic acid are added and the mixture is stirred for ca. 2 hours at ca. 80°C. 4 ml of water are added to the mixture obtained and the resulting mixture is cooled to ca. 5 °C. The pH of the solution is adjusted to ca. 10 by addition of 2 N aqueous sodium hydroxide solution and the resulting mixture is stirred for ca. 1 hour. A solid is formed, filtrated off, washed with water and dried. 6-O-methyl-erythromycin A (clarithromycin) is obtained.

Example 22

a) 2'-4 "-O-bis(trimethylsilyl)-9-O-(2-methoxyethoxymethyl)-eryhtomycin A-9-oxime

8.81 g of roxithromycin are dissolved in 50 ml of ethyl acetate and 4.45 ml of hexamethyldisilazane and 44 mg of saccharin are added. The mixture is heated under reflux for ca. 150 minutes and cooled to room temperature. The ethyl acetate solution obtained is washed with 100 ml of a 5% aqueous sodium hydrogen carbonate solution and with 100 ml of water, dried over anhydrous magnesium sulphate, filtered and evaporated to dryness.
8.07 g of 2'-4 "-O-bis(trimethylsilyl)-9-O-(2-methoxyethoxymethyl)-eryhtomycin A-9-oxime are obtained.
IR (KBr, cm^{-1}): 3470, 2970, 2938, 2827, 1738, 1458, 1380, 1287, 1251
13C-NMR ($CDCl_{3,\ 75.4\ MHz}$) : 1.04 (Me_3Si), 1.15 (Me_3Si)

b) 2'-4"-O-bis(trimethylsilyl)-9-O-(2-methoxyethoxymethyl)-6-O-methyl eryhtomycin A-9-oxime

To a solution of 3.96 g of 2'-4 "-O-bis(trimethylsilyl)-9-O-(2-methoxyethoxymethyl)-eryhtomycin A-9-oxime in 50 ml of DMSO/THF (1:1) cooled at ca. 0/5°, 1.05 g of powdered potassium hydroxide and 1.0 ml of methyl iodide are added. The mixture obtained is stirred for ca. 45 minutes at 0/5 °. 6 ml of methylamine (40 % in water), 100 ml of water and 60 ml of ethyl acetate are added. A two-phase system is obtained. The organic phase is decanted and the aqueous phase is extracted with 50 ml of ethyl acetate. The combined organic phases are dried over magnesium sulphate, filtered and evaporated to dryness.

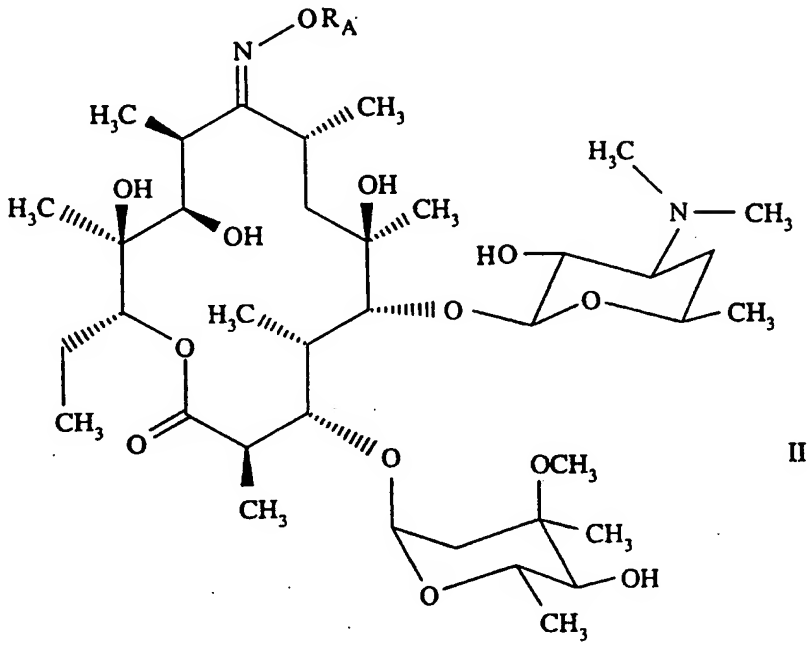
4.4 g of 2'-4"-O-bis(trimethylsilyl)-9-O-(2-methoxyethoxymethyl)-6-O-methyl eryhtomycin A-9-oxime in the form of a foam are obtained.

6-O-methyl erithromycin A oxime may be obtained from 2'-4"-O-bis(trimethylsilyl)-9-O-(2-methoxyethoxymethyl)-6-O-methyl eryhtomycin A-9-oxime as conventional, e.g. as described in the description above.

Claims

1. Erythromycin A oxime wherein the hydroxyl group of the oxime group is in reacted form resulting from reaction with a strong organic base or with a silylation agent.

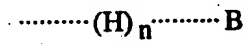
2. A compound of formula



II

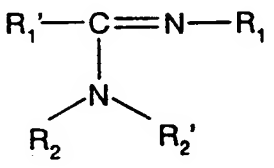
wherein R_A denotes

a silyl group; or a group of formula



wherein

(i) n = 1 and B is a compound of formula

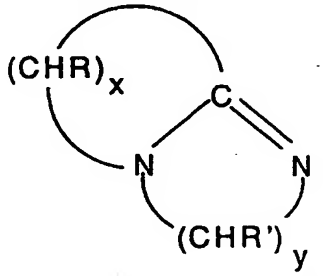


III

wherein R_1, R_1', R_2 and R_2' independently of each other denote hydrogen or an aliphatic or aromatic group; or R_1 and R_1' independently of each other denote an

aliphatic or aromatic group and R_2 and R_2' together with the nitrogen atom denote a ring or ring system,

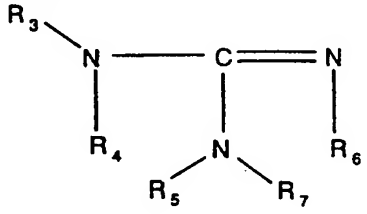
(ii) n = 1 and B is a compound of formula



IV

wherein R and R' independently of each other denote hydrogen or an aliphatic or aromatic group; x denotes 3, 4, or 5 and y denotes 2, 3 or 4;

(iii) n = 1 and B is a compound of formula



V

wherein R_3, R_4,R_5, R_6 and R_7 denote independently of each other hydrogen or an aliphatic or aromatic group;

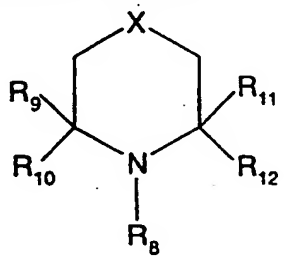
or R_3 is as defined above; and

either R_4 and R_5 together denote (C_1-$_4$)alkylidene and R_6 and R_7 independently of each other denote hydrogen; or an aliphatic or aromatic group;

or R_4 and R_5 together denote (C_1-$_4$)alkylidene and R_6 and R_7 together denote (C_1-$_4$)alkylidene;

or R_6 and R_7 together denote (C_1-$_4$)alkylidene and R_4 and R_5 independently of each other denote hydrogen or an aliphatic or aromatic group;

(iv) n = 1 and B is a compound of formula



VI

wherein R_8, R_9, R_{10}, R_{11} and R_{12} independently of each other denote hydrogen or an aliphatic or aromatic group, and X denotes CH_2, NH, O or S;

(v) n = 0 and B is a group of formula

$$Z^+R_{13}R_{14}R_{15}R_{16} \qquad \text{VII}$$

wherein Z denotes nitrogen, and R_{13}, R_{14}, R_{15}, and R_{16} independently of each other denote an aliphatic or aromatic group.

3. Erythromycin A oxime wherein the hydroxyl group of the oxime group is in reacted form resulting from reaction with a strong organic base which shows a molecular peak of an oximate of erythromycin A oxime of formula I with a strong organic base in mass spectroscopy determination.

4. A process for the production of erythromycin A oxime in the form of an oximate with a strong organic base, comprising reacting erythromycin A oxime with a strong organic base, and, if desired isolating erythromycin A oxime in the form of an oximate.

5. Erythromycin A oxime wherein the hydroxy group in the hydroxyimino group is silylated.

6. A process for the production of erythromycin A oxime wherein the hydroxy group in the hydroxyimino group is silylated comprising silylating a compound of formula II wherein R_A denotes a group of formula

$$\cdots\cdots(H)_n\cdots\cdots B$$

wherein n and B are as defined in claim 2.

7. A process for the production of a compound of formula II of claim 2, wherein R_A denotes silyl and wherein the hydroxy groups in position 2' and 4" of the ring system are silylated, comprising reacting a compound of formula II, wherein R_A denotes a a silyl group with a silylating agent.

8. Use of Erythromycin A oxime wherein the hydroxyl group of the oxime group is in reacted form resulting from reaction with a strong organic base or with a silylation agent.

as an intermediate in the production of macrolides of the erythromycin type.

9. Use according to claim 8 in the production of roxithromycin, clarithromycin, or azithromycin.

10. A process for the production of an O-alkylated erythromycin A oxime comprising reacting a compound of formula II according to claim II, wherein R_A denotes a group of formula

$$\cdots\cdots(H)_n\cdots\cdots B$$

wherein n an B are as defined in claim 2 with a compound of formula

Alk-L

wherein Alk denotes an alkyl group and L denotes a leaving group.

11. A process according to claim 10 for the production of roxythromycin wherein Alk denotes the group $CH_3OC_2H_5OCH_2$-.

12. A process for the production of clarithromycin comprising the steps
    i) silylating the hydroxy groups in position 2' and 4'' in the ring system of an erythromycin A oxime wherein the hydroxy group of the oxime is alkylated,
    ii) methylating the hydroxy group in position 6 of the ring system in a compound obtained in step i) to obtain erythromycin A oxime wherein the hydroxy group of the oxime is alkylated and wherein the hydroxyl groups in position 2' and 4'' are silylated and wherein the hydroxyl group in position 6 is methylated; and
    iii) removing the silyl groups from and deoximating a compound obtained in step ii) to obtain clarithromycin.

13. A process for the production of clarithromycin comprising the steps
    i) silylating the hydroxy groups in position 2' and 4'' in the ring system of roxythromycin,
    ii) methylating the hydroxy group in position 6 of the ring system in a compound obtained in step i) to obtain roxythromycin wherein the hydroxyl groups in position 2' and 4'' are silylated and wherein the hydroxyl group in position 6 is methylated; and

iii) removing the silyl groups from and deoximating a compound obtained in step ii) to obtain clarithromycin; e.g. and isolating clarthromycin.

14. A process for the production of clarithromycin comprising the steps

i) producing roxythromycin by reacting a compound of formula II, wherein R_A denotes a group of formula

$$\cdots\cdots\cdots(H)_n\cdots\cdots\cdots B$$

wherein n an B are as defined above with a compound of formula

$$CH_3OC_2H_5OCH_2\text{-}L$$

wherein Alk denotes an alkyl group and L denotes a leaving group,

ii) silylating the hydroxy groups in position 2' and 4" in the ring system of roxythromycin,

iii) methylating the hydroxy group in position 6 of the ring system in a compound obtained in step i) to obtain roxythromycin wherein the hydroxyl groups in position 2' and 4" are silylated and wherein the hydroxyl group in position 6 is methylated; and

iv) removing the silyl groups from and deoximating a compound obtained in step ii) to obtain clarithromycin.